

USSN: 09/719,410

Rsp. Dated 5/10/05

Reply to Office Action of 12/27/04 and Advisory Action of 4/20/05

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Amendments to the Specification:

Please replace the paragraph beginning on page 6, line 10, with the following amended paragraph:

β -cell function is quantified by normalized spectral power. Spectral power measures β -cell function which does not rely on adjustment for insulin sensitivity. The inventors have found that in subjects with IGT, GLP-1 improves spectral power into a normal range. The spectral power profiles indicated that the entrainment or close coordination of plasma glucose and insulin secretion oscillations ~~was~~ were restored to normal levels in IGT subjects after administration of GLP-1. This improvement in the oscillatory pattern of insulin secretion is important for the maintenance of normal glucose homeostasis. For example, it has been shown that insulin infusions that mimic the ultradian oscillations within a period of 120 minutes are more effective than constant infusions of insulin in the reduction of plasma glucose concentrations (27).

Please replace the paragraph beginning on page 14, line 7, with the following amended paragraph:

The studies described herein were performed in 10 subjects who were divided into two groups on the basis of their plasma glucose response to an oral glucose tolerance test using the criteria of the World Health Organization (24) to define the degree of glucose tolerance. Five subjects had IGT, and five subjects had NIDDM. The gender, age, body mass index (~~BMI~~) (BMI), basal levels of fasting glucose, 2 hour glucose, fasting insulin, and HBA1c for each subject are presented in Table 2. Diabetic subjects were older than those with IGT, but the groups were matched for by BMI. Mean fasting glucose levels and glycosylated hemoglobin concentrations were lower in the IGT group compared to subjects with NIDDM. Fasting insulin levels did not differ between the groups.

Please replace the paragraph beginning on page 15, line 21, with the following amended paragraph:

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Plasma glucose levels were measured by the glucose oxidase technique (YSI, 1500 G, Schlag Company, Bergisch-Gladbach, Germany). The coefficient of variation of this method was <2%. Plasma insulin was measured by the Abbott IMx Microparticle Enzyme Immunoassay. The average intraassay coefficient of variation was 5%. Plasma C-peptide was measured as previously described in (22), Faber OK, Binder C, Markussen J, Heding LG, Naithani VK, Kuzuya H, Blix P, Horwitz DL, Rubenstein AH. Characterization of seven c-peptide antisera. *Diabetes* 27, Suppl 1:170-177, 1978. The lower limit of sensitivity of the assay was 0.02 pmol/ml and the intraassay coefficient of variation averaged 6%. Glucagon was measured by using a commercially available radioimmunoassay kit (Biermann, Bad Nauheim, Germany) and the intraassay coefficient of variation averaged 8%. IR-GLP-1 was measured using the specific polyclonal antibody GA 1178 (Affinity Research, Nottingham, UK) (23). It has 100% reactivity with GLP-1 (1-36) amide and the truncated GLP-1 (7-36) amide. Immunoreactive GLP-1 like material was extracted from plasma samples on C-18 cartridges employing acetonitrile for elution of the samples. The detection limit of the assay was 2 fmol/tube. The antiserum did not crossreact with GIP, pancreatic glucagon, glicentin, oxyntomodulin or GLP-2. Intra- and interassay coefficients of variation were 3.4% and 10.4%, respectively.

Please replace the paragraph beginning on page 16, line 15, with the following amended paragraph:

Standard kinetic parameters for C-peptide clearance adjusted for age, sex and body surface area were utilized (24), Van Cauter E, Mestrez F, Sturis J, Polonsky KS. Estimation of insulin secretion rates from C-peptide levels: comparison of individual and standard kinetic parameters for C-peptide clearance. *Diabetes* 41:368-377, 1992. These parameters were used to derive, in each 15 minute interval between blood sampling, the ISR from the plasma C-peptide concentrations by deconvolution as previously described (25,26).